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Eosinophilic dermatosis of hematologic malignancy: A retrospective cohort of 37 patients from an Italian center

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Title: Eosinophilic dermatosis secondary to hematologic malignancies: a retrospective cohort of 37 patients from an Italian centre.

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To the Editor,

Eosinophilic dermatosis of hematologic malignancy (EDHM) is a non-specific skin disease primarily associated with chronic lymphocytic leukemia (CLL).[1,2,3] Despite being a common disease in the hematology setting, often misdiagnosed as an exaggerated reaction to mosquito bites,[2] there is a shortage of dermatology-oriented reports. Here we report on a retrospective case series of EDHM carried out in our department from November 2014 to January 2017. The main results of the study are listed in table 1.

We identified 37 patients on the basis of the proposed EDHM diagnosis criteria, which include: i) known history of onco-hematological disease, ii) recurrent episodes of papules, nodules, urticarial plaques or blisters with intense pruritus, iii) eosinophilic infiltration upon histopathology, and iv) exclusion of other causes of tissue eosinophilia.[1] The majority suffered from indolent B-cell disorders, primarily B-CLL (51%) and various types of B-cell non-Hodgkin lymphomas (30%), whereas acute leukemia was observed in four patients (10%). At the time of EDHM onset, only a minority of them (25%) underwent chemotherapy due to active/progressive disease.

The eruption was widespread , albeit mostly occurring on the lower (90%) and upper limbs (79%). However, over half of the cases had lesions on the trunk and 25% reported painful lesions on the face, scalp, and neck.

The majority of the patients presented with pruritic erythematous papules, plaques, and nodules with a smooth surface and color ranging from slightly pink to bright red, or more cyanotic hues. In one third of cases, tense blisters resembling Bullous Pemphigoid (BP) were evident, especially on the legs (Figure 1A).

Skin specimens showed variably dense, mainly perivascular lymphohistiocytic and eosinophilic infiltrates in the upper and mid-dermis in the majority of cases (80%), extending to the deep dermis and subcutaneous fat in 20% of cases. In two cases, the histologic features resembled those

of Wells syndrome, revealing numerous eosinophils with flame figures in the deep dermis. Dermal-epidermal detachment was observed in 10 cases, raising suspicion of BP. In these cases, direct immunofluorescence was negative. No relevant epidermal changes were found, except for spongiosis in two specimens (Figure 1B).

Almost all patients showed some clinical benefit with the proposed treatment: most of the patients were treated with systemic steroids with/without concomitant topical steroids. A minority of patients achieved clinical improvement with other regimens, including doxycycline with/without nicotinamide and UVA1 phototherapy. The overall response rate was 93%. However, in many cases (63%) the response was short-lived and the patient suffered a relapse.

Our study shows that EDHM potentially occurs in a wide range of hematologic cancers, with differing biological behavior and of either lymphoid or myeloid origin. Due to its clinical/pathological heterogeneity and its tendency to persist over long periods, it may represent both a diagnostic and therapeutic challenge. The overlap with BP should be kept in mind to avoid misdiagnosis and may have led to an overestimation of the BP incidence in this setting.[1,4,5] Besides systemic steroids, doxycycline, nicotinamide, and UVA1 phototherapy could be effective therapeutic alternatives considering their lower long-term toxicity, but this data warrants further prospective investigations.

To conclude, we believe that EDHM is an underestimated disorder. Although there is no evidence to suggest that EDHM has a negative impact on the prognosis for the underlying malignancy, it has significant negative implications for patients given its uncomfortable symptoms and chronic, relapsing course. The main limitation of this study is its retrospective design. Further pathophysiological insights and long-term prospective studies are advisable to gain a better understanding of this disorder and optimize patient management.

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Table 1. Summary of the main results of the study, including demographic, clinical and therapeutic data in patients with eosinophilic dermatosis of haematological malignancies (EDHM).

Characteristic	**Value**
Enrolled patients	37
Male	17 (46%)
Female	20 (54%)
Associated malignancies	
B-cells chronic lymphocytic leukaemia	19 (51%)
B-cells non Hodgkin lymphoma	11 (30%)
Multiple myeloma/monoclonal gammopathy of undermined significance	2 (5%)
Acute leukemia	4 (10%)
Aggressive T-cell lymphoma	1 (2.5)

Age at time of hematologic diagnosis (years)	Mean = 66, range = 40-88, median = 67
Age at time of EDHM diagnosis (years)	Mean = 70, range = 41-89, median = 74
Latency between hematological diagnosis and EDHM (months)	Mean = 57, median = 40, range = 5-191
Follow up (months)	Mean = 8.7, median = 5, range = 0-34
Previous exposure to chemotherapy	27/34 (80%)
On chemotherapy at time of skin rash	7/34 (20%)
Duration of rash (months)	Mean = 7, median = 3.5, range = 1-34
Seasonality	
Spring	13/37 (35%)
Summer	10/37 (27%)
Autumn	9/37 (24%)
Winter	5/37 (13%)
Involved sites	
Head/neck	9/37 (24%)
Trunk	20/37 (54%)
Upper limbs	30/37 (81%)
Lower limbs	34/37 (91%)
Type of lesions	
Papules	28/37 (75%)
Plaques	17/37 (45%)
Nodules	15/37 (40%)
Vesicles	7/37 (19%)
Blisters	12/37 (32%)
Therapy	
Prednisolone 0.5 mg/kg/day	16/34 (46%)
Prednisolone 1.0 mg/kg/day	8/34 (23%)
Topical steroids	12/34 (35%)
Oral antihistamines	6/34 (18%)

Cyclosporine	1/34 (3%)
UVA1	2/34 (6%)
Doxycicline	4/34 (12%)
Oral nicotinamide 1g/die	4/34 (12%)
Overall response rate	28/30 (93%)
Complete responses	12/30 (40%)
Partial Responses	16/30 (53%)
No Response	2/30 (7%)
Relapse rate	12/19 (63%)
Mean relapse free interval (months)	Mean = 5, median = 4, range = 1- 14
On chemotherapy at time of relapse	3/12 (25%)

Figure legend

Figure 1. A: Distinct clinical presentations of eosinophilic dermatosis of hematologic malignancy. a) light pink plaque on a leg resembling Wells Syndrome. b-c) multiple erythematous papules and nodules on the head and neck. d) tense blisters, some hemorrhagic, on the forearm. e) multiple, monomorphic, centered erythematous papules on the trunk that persisted for months. B: Distinct histopathologic presentation of eosinophilic dermatosis of hematologic malignancy. (a) Extensive intra and subepidermal edema with dermal-epidermal detachment, and an intense, perivascular, mixed inflammatory infiltrate with numerous eosinophils, extending from the upper into the reticular dermis, resembling Wells syndrome (hematoxylin and eosin, magnification 10x). At higher magnification, it becomes possible to observe flame figures, consisting of hypereosinophilic collagen fibers surrounded by degranulated eosinophil granulocytes (hematoxylin and eosin, magnification x40). (b) Dermal-epidermal unilocular detachment. Mixed-type inflammatory infiltrate with a few superficial perivascular and dermal eosinophilic granulocytes (hematoxylin and eosin, magnification x10). (c) Acanthosis and mild epidermal spongiosis. Edema of the upper dermis. Presence of a moderate, inflammatory interstitial infiltrate consisting of eosinophilic granulocytes in the upper and mid-dermis (hematoxylin and eosin, magnification x20).